

**PCT**

REC'D 10 AUG 2004

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

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(PCT Article 36 and Rule 70)

Rec'd PCT/PTO 17 FEB 2005

Applicant's or agent's file reference 150371/KB	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/CZ 03/00046	International filing date (day/month/year) 15.08.2003	Priority date (day/month/year) 22.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/00		
Applicant PLIVA-LACHEMA A.S.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 5 sheets, including this cover sheet.  
  
☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
  
 These annexes consist of a total of 2 sheets.

- This report contains indications relating to the following items:
  - ☒ Basis of the opinion
  - ☐ Priority
  - ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - ☐ Lack of unity of invention
  - ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - ☐ Certain documents cited
  - ☐ Certain defects in the international application
  - ☐ Certain observations on the international application

Date of submission of the demand  15.12.2003	Date of completion of this report  09.08.2004
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer  Hedegaard, A  Telephone No. +49 89 2399-8644  

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/CZ 03/00046

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-17 as originally filed

**Claims, Numbers**

1-4 received on 14.06.2004 with letter of 11.06.2004

5, 6 received on 17.06.2004 with letter of 15.06.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/CZ 03/00046**

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**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes: Claims	1-6
	No: Claims	
Inventive step (IS)	Yes: Claims	1-6
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-6
	No: Claims	

**2. Citations and explanations**

**see separate sheet**

**Re Section V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following documents:

D1: International Journal Of Pharmaceutics (1996), 144(1), p. 107-114  
D2: SK-B-279067  
D3: US-A-5783205  
D4: EP-A-0290983

D1 discloses (see Table 1 on p. 108) vehicles consisting of a terpolymer prepared by polycondensation of glycolic acid (45.06 mol), mannitol (0.9 mol) and DL-lactic acid (45.05 mol).  $T_g$  is 20°C,  $M_n$  is 2.20 kDa and  $M_w$  is 3.95 kDa. An active compound (BSA) is entrapped in said vehicles (see abstract on p. 108 of D1).

D2 discloses (see example 8 on p. 4) compositions comprising an antimicrobial compound and a carrier consisting of a terpolymer prepared by polycondensation of glycolic acid, mannitol and DL-lactic acid (4,0 . 5,6 . 0,4).  $T_g$  is 20°C,  $M_n$  is 2200 and  $M_w$  is 3950.

D3 discloses (see claim 1 and col. 7, l. 25-29) a composition for delivery of drugs comprising the drug and a carrier such as an oligomer of glycolic acid and/or lactic acid and glycerol. Reference is made to D4 in which said carriers are described.

D4 discloses (see Table 1) polyester-oligomers of lactic acid and glycerol (e.g. in a ratio of 10:1). The oligomers have molecular weights in the range from 200 to 1500 (p. 2, l. 49 of D4).

2. The subject-matter of claims 1-5 (composition) and 6 (preparation) is novel (Art. 33(2) PCT) since none of the above-mentioned documents have disclosed a biodegradable composition comprising an antitumour agent and a carrier-system as defined in the present claim 1.
3. The problem of the present application was to provide biodegradable compositions, implantable directly into a target tissue, with prolonged release of antitumour agent.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/CZ 03/00046

This problem is solved by the composition according to claim 1 defining a specific oligoester carrier and a specific system in the form of homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion.

The subject-matter of claim 1 differs from D1 (closest prior art) in that it is a plastic monolithic system (homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion) and not microspheres as in D1. Thereby a specific release mechanism is obtained. There was no hint in D1 (or any of the other cited documents) leading to the composition of present claim 1. Therefore, the subject-matter of claims 1-6 is considered to involve an inventive step (Art. 33(3) PCT).

## C L A I M S

1. Biodegradable antitumour composition with prolonged release of an antitumour agent destined for the administration into tissues, characterised in that it comprises at least one antitumour agent and a carrier, consisting of biodegradable oligoester, having the numeric mean relative molecular mass  $M_n$  from 650 to 7 500, the mass mean relative molecular mass  $M_w$  from 800 to 10 000 and the glass transition temperature  $T_g$  from  $-35$  to  $45$  °C, and which is prepared by polycondensation reaction of polyhydric alcohol containing at least 3 hydroxy groups with at least one aliphatic  $\alpha$ -hydroxy acid in the molar ratio of polyhydric alcohol to aliphatic  $\alpha$ -hydroxy acid being from 0.5:99.5 to 12:88, wherein the central molecule of biodegradable oligoester is a polyhydric alcohol, to the hydroxy groups of which chains created from several molecules of at least one aliphatic  $\alpha$ -hydroxy acid are bound by ester bonds, and in that it is in the form of homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion.
2. The composition according to claim 1, characterised in that it further comprises at least one liquid biocompatible plasticizer, wherein the weight ratio of at least one biocompatible plasticizer to biodegradable oligoester is from 1:20 to 9:10.
3. The composition according to claim 2, characterised in that the liquid biocompatible plasticizer is soluble in the carrier and imperfectly soluble or insoluble in water.
4. The composition according to claims 1 to 3, characterised in that it further comprises at least one agent influencing the kinetics of the release of the antitumour agent.

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5. The composition according to claim 1 to 4, characterised in that it further comprises at least one stabilizer of the antitumour agent or carrier.

6. The preparation of the antitumour composition according to claims 1 to 5, characterised in that an antitumour agent, a carrier, and optionally a liquid biocompatible plasticizer, an agent influencing the kinetics of the release of the antitumour agent, a stabilizer of the antitumour agent or a stabilizer of the carrier are heated to the temperature of 35 to 75 °C and mixed.

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17-06-2004